Acute kidney injury is a major risk in coronavirus disease 2019 infected patients receiving extracorporeal membrane oxygenation (ECMO): single-center experience from the MENA region

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Background
Some reports criticizing the role of extracorporeal membrane oxygenation (ECMO) on the outcome of critically ill coronavirus disease 2019 (COVID-19) infected patients. Worldwide medical organizations- during early phase of pandemic- considered ECMO if standard of care treatment failed. To evaluate risk factors associated with the outcome of patients admitted to intensive care units with COVID-19 infection for ECMO procedure.

Methods
In such an observational study, patients infected with COVID-19 who needed ECMO in Kuwait from March 1, 2020 to December 31, 2021 were enrolled. We recorded the following information for all patients: socio-demographics, clinico-laboratory factors, radiological results, and management strategies. Furthermore, major complications during ECMO procedure were reported especially bleeding/thrombotic events, blood product transfusions and acute kidney dysfunction. Final outcome was recorded with special stress on ECMO duration, ICU stay, patient outcome, and respiratory status on discharge.

Results
The majority of patients (58.5%) in our cohort survived. Most of the nonsurvivors were males ($P = 0.046$), older ($P = 0.01$), with higher mean platelet volume, D-dimer and mean CO_2 ($P < 0.05$). The majority of nonsurvivors (56.9%) had chest computed tomography findings matched with COVID-19 ($P = 0.028$). Besides, most of the nonsurvivors were hemodynamically unstable on vasopressors (89.2%) or developed AKI during the procedure of ECMO (78.5%), ($P < 0.001$, 0.012, respectively). The use of biological agents had improved the survival (75 vs. 49.5% in those who did not receive it, $P = 0.038$). ECMO duration correlated positively with patient age ($P = 0.012$). Besides, postdischarge O_2 supplementation or CPAP was needed in 48.1 and 11.4%, respectively.

Conclusion
ECMO must be indicated for critically sick COVID-19 infected cases with respiratory failure not responding to standard of care (SOC) management. We found that young age and treatment with biological agents were good omens for surviving while the mortality risk factors were diabetes, shock, AKI during the procedure, CT findings matched with COVID-19 pneumonia, and high arterial CO_2.

Keywords:
coronavirus disease 2019, extracorporeal membrane oxygenation, ICU, mortality, respiratory failure

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Introduction

All types of oxygen therapies-invasive and non-invasive-primarily combined with prone positioning were beneficial in most cases with SARS-CoV-2 virus coronavirus disease 2019 (COVID-19) [1]. Managing these critically ill patients is further complicated by potential secondary infections, acute myocardial disease, and thrombophilia, with or without pulmonary embolism [2–4].

Previous experience with the pandemic in different European centers was almost the same. The mean number of managed-cases with the procedure of extracorporeal membrane oxygenation (ECMO) before COVID-19 was 55 every year. This number significantly increased with COVID-19 patients, ranging from 136 to 385 in France, United Kingdom, Germany, Spain, and Italy [5]. Noting that the earliest research works on ECMO reported very high mortality rates in small sample-sized COVID-19 cases [6]. However, this result was influenced by previous evidence from patients suffering from acute respiratory distress syndrome without COVID-19 infection [7,8].

Even before the pandemic, international medical organizations are advising ECMO if traditional treatment fails [9–11]. In multicenter observational studies, the outcomes among ECMO treated- COVID-19 patients were similar to patients without COVID-19-related acute respiratory distress syndrome. The estimated 90-day survival rate was recorded more than 60% (95% confidence interval 34.4–40.4) by the voluntary international registry of the Extracorporeal Life Support Organization (ELSO) [9–15]. The impact of ECMO support remains uncertain, because no randomized controlled clinical trials were conducted to evaluate the outcomes of using invasive mechanical ventilation with ECMO versus without in COVID-19 patients [6].

Ramanathan *et al.,* in their meta-analysis, assessed 22 studies recruited more than 1890 COVID-19 patients on ECMO. They reported an in-hospital mortality of 37%, with a 95% confidence interval of 32.2–42.0. A mortality rate of 50% or greater was reported in subsequent studies. These studies did not clarify whether there have been changes in mortality over time or the reasons for any such changes [16].

Barbaro *et al.* reported an increase in 3-month mortality rate from 37% (before May 1, 2020) to 52% (after May 1, 2020) among COVID-19 patients supported with ECMO and six days increase in median duration of ECMO support. Patients treated after May 1, 2020, were more likely to receive corticosteroids and had a higher chance of resistant disease. The study also reported a higher mortality rate in medical centers which are lacking ECMO support for COVID-19 patients [6].

Aim

To assess risk factors associated with the outcome of ECMO procedure in ICU infected COVID-19 patients.

Patients and methods

In this retrospective observational study, we included all ECMO-treated, critically ill COVID-19-positive patients who were admitted to our hospital between May 2020 and 2021. During this time, 120 ECMO procedures were performed in our center. Patients were categorized into: survivors comprised group 1 and nonsurvivors comprised group 2. Our institution's electronic health record system was used to collect the data. Socio-demographics including sex, age, comorbidities, and smoking history were collected. We also included other clinical-laboratory parameters with special stress on routine investigations, lactate dehydrogenase, ferritin, blood gases analysis, D-dimer, in addition to pan cultures; positive growth anywhere. In addition, we collected chest imaging results and other lines of treatment like anticoagulants, corticosteroids, biological therapies, antivirals, and antibiotics. Any complications or major events during ECMO were also reported, especially thrombotic or bleeding events, blood and or platelet transfusion, with or without acute kidney injury (AKI). The final outcome upon discharge concerning the need for oxygen was reported. This study was approved by the ethical committee of ministry of health of Kuwait. (2020/1467).

Procedure of extracorporeal membrane oxygenation

Preferably, the right femoral vein was accessed over the left one for drainage cannulation (commonly more curved), and regarding backflow cannulation, we used either the femoral artery for Venoarterial (VA)-ECMO, and for Venovenous (VV)-ECMO, we used the jugular vein. Our ICU colleagues reviewed the patient's history and performed a bilateral femoral vascular ultrasound to assess the patient's eligibility for ECMO.

The guide wires and drainage cannulations were located using ultrasound guidance. VA-ECMO helped to prevent circulatory failure by enhancing oxygen delivery and supply. To ensure good cerebral perfusion in external cardiopulmonary resuscitation patients, a blood flow of (4 ± 0.5 L/min) was established aiming at a mean arterial pressure of 65 ± 5 mmHg. The tip of the drainage catheter was kept in the left atrium.

The ultrasound Doppler was used to monitor the aortic valve's blood flow closely. This procedure was crucial to prevent increased afterload or left atrial or ventricular thrombosis caused by the high blood flow in VA-ECMO. We gave priority to continuous renal replace ment therapy to sustain stabilization of the internal environment, except if the patient did not have any worsening of his kidney function or oliguria. In respiratory failure requiring VV-ECMO, low-volume ventilatory strategies and prone positioning were performed before and after ECMO initiation. We were keeping the tip of the drainage cannulation in the inferior vena cava (IVC) to minimize re-circulation. Both oxygen concentration and flow of VV-ECMO were optimized. As an integral part

of our procedure, we seek an O_2 saturation between 88 and 95% and a PCO_2 (partial pressure of carbon dioxide) of 35–45 mmHg. In addition, evaluating bedside echocardiography and readiness for ECMO weaning are daily basics in our center. Moreover, regular attempts with the sweep gas turned off were needed before VV-ECMO removal. According to the Extracorporeal Membrane Oxygenation for Severe Acutr Respiratory Distress Syndrome (EOLIA) study, the VV-ECMO weaning criteria were: Partial pressure of oxygen (PaO_2) greater than or equal to 60 mmHg, SaO_2 greater than or equal to 90%, with FiO_2 less than or equal to 60%; PH greater than or equal to 7.36 or $PaCO_2$ less than or equal to 50 mmHg, with respiratory rate less than or equal to 28/min; Pplat less than or equal to 28 cmH_2O; with no signs of acute corpulmonale [7].

Statistical analysis

The program of Statistical Package for Special Science (SPSS, IBM, Armonk, New York, United States of America) version 26 was utilized for data analysis. Categorical variables were presented as frequencies and percentages while the continuous variables were presented as mean ± SD. We used *T*-test to compare data with normal distribution, and Mann–Whitney *U* test for skewed data. Categorical data were cross-tabulated using χ^2 test. Bivariate techniques were used for initial evaluation of contrasts and a *P* value less than 0.05 was significant.

Results

A total of 120 cases with COVID-19 diagnosed by the PCR test, needing ICU admission for ECMO procedures were enrolled. We compared survivors ($n = 64$) vs. nonsurvivors ($n = 56$) regarding demographics, indications of ECMO, laboratory parameters and possible risk factors. All patients required invasive ventilation with high parameters before ECMO.

Demographics

Patient characteristics and demographics were demonstrated (Table 1). Significantly, the mean age of survivors was lower than nonsurvivors (37.5 ± 10.9 vs. 43.6 ± 8.7 respectively, $P = 0.006$). Patients younger than 40 years were significantly more prevalent in group 1, while the middle age group was more prevalent among the nonsurvivors ($P = 0.034$). The majority of patients in the two groups were males 35 (54.7%) and 40 (71.4%), respectively, but without ranking to significance ($P = 0.06$). Both groups were also, comparable regarding their nationality.

In group 2, we found that only three (5.35%) patients were current smokers. The most predominant COVID-19 risk factors encountered in our cohort were hypertension, obesity, kidney function status, chronic obstructive pulmonary disease (COPD), and ischemic heart disease (IHD) had no significant difference were among the groups ($P > 0.05$). However, we observed

Table 1 Demographic and clinical characteristics

Variables	Post-ECMO survivors (*n*=64), *n* %	Post-ECMO nonsurvivors (*n*=56), *n* %	*P*
Age (years)*	37.5±10.9	43.6±8.7	0.006
Age group			0.034
<40 years	36 (56.3)	20 (35.7)	
40–<60 years	25 (40.6)	35 (62.5)	
>60 years	2 (3.1)	1 (1.8)	
Sex			0.059
Male	35 (54.7)	40 (71.4)	
Female	29 (45.3)	16 (28.6)	
Nationality			0.10
Kuwaiti	34 (53.1)	38 (67.9)	
Non-Kuwaiti	30 (46.9)	18 (32.1)	
COVID-19 risk factors			
Smoking	0	3 (5.4)	0.06
DM	10 (15.6)	19 (33.9)	0.024
HTN	11 (17.2)	17 (30.4)	0.10
IHD	2 (3.1)	1 (1.8)	0.61
Obesity	4 (6.3)	1 (1.8)	0.20
Kidney transplant	2	3	0.57
COPD	3	5	0.39
Kidney Function			0.71
Normal	39 (60.9)	36 (64.3)	
Acute kidney injury	22 (34.4)	19 (33.9)	
Chronic kidney disease	39 (4.7)	1 (1.8)	
ICU stays (days)*	31.9±29.8, 28	28.8±25.5,25	0.58

*Mean±SD.

that diabetics were significantly more prevalent among group 2 patients ($P = 0.024$).

All patients had an admission Chest radiography or at the time of diagnosis (Table 2). More than 53% of patients in group 2 had high-resolution chest computed tomography with compatible findings with COVID-19 bronchopneumonia. This percentage was significantly higher than that reported in group 1 (29.68%), showing the same findings.

The results of chest imaging showed multifocal patchy opacifications bilaterally in 48 (40%) cases. Nonetheless, all patients needed mechanical ventilation before ECMO. No significant difference was found regarding AKI before ECMO procedure between the two groups ($P > 0.05$).

Regarding laboratory investigations and radiological features (Table 2) we observed comparable number of patients with positive bacterial cultures (blood and sputum) in both groups ($P > 0.05$). We observed that laboratory markers suggesting bacterial co-infection (evidenced by high procalcitonin) was higher in group 1 (15.66 ± 41,0.5 vs. 6.9 ± 30.1,0.33) but this did not rank to significance ($P > 0.05$). During the ECMO procedure, leukopenia (not more than 4000 cells/μl) was found in 11.6% of cases (eight cases in group 1 and six cases in group 2), while leukocytosis (more than 11000 cells/μl) was confirmed in 32.5% (25 cases in group 1 and 14 cases in group 2). Moreover, we observed that hematological complications (either thrombotic or bleeding events) were comparable in the two groups regarding ($P > 0.05$). Moreover, there is no statistically significant difference between the two groups concerning other laboratory parameters apart from PCO_2 which was significantly higher in the nonsurvivors ($P = 0.014$). From Tables 1 and 2, we can observe that the kidney function was stable in most patients before ECMO procedure (33/53 vs. 36/56).

The management plan was nearly identical in the two groups (Table 3). A higher percentage of patients in group 2 received steroid therapy (80.4 vs. 68.7%, $P = 0.18$), anticoagulation (89.3% in group 2 vs. 79.7% in group 1, $P = 0.11$), antiviral therapies (17.9 vs. 15.6%, $P = 0.81$), antibacterial (87.5 vs. 85.9%, $P = 0.50$), blood transfusion (50 vs. 46.9%, $P = 57$) and plasma transfusion (8.9 vs. 6.2%, $P = 0.70$) but this did not rank to significance. However, higher number of cases received biological treatment in group 1 (21.9 vs. 8.9%, $P = 0.04$).

Hemodynamic instability (shock) was reported significantly more frequently in patients of group 2 (50 vs. 35 cases in group 1, P=<0.001). Unfortunately, a higher number of patients developed

Table 2 Computed tomography and laboratory investigations post-ECMO procedure

Variables	Post-ECMO survivors (*n*=64) Mean±SD, median	Post-ECMO nonsurvivors (*n*=56) Mean±SD, median	*P*
Platelets	253±168, 245	236.6±112,275	0.51
Mean platelet volume	10.3±2.1	10.3±1.7	0.89
Hemoglobin	87.9±48,103	89.2±52,113	0.89
Total leucocytic count	10.8±7.4	6.9±9.2	0.64
*Normal	31 (48.4)	36 (64.3)	0.18
*Low	8 (12.5)	6 (10.7)	
*High	25 (39.1)	14 (25)	
Lymphocyte count	9.5±7.9	10.4±7.8	0.55
Serum creatinine	94±98,65.5	95.4±69,72	0.93
Serum sodium	135±18.4, 138	135.2±14,137	0.96
Serum potassium	4.1±0.46,4	4.3±0.61	0.23
Lactate dehydrogenase	549.5±353,522	561.4±446,472	0.87
Ferritin	540.7±±727,220	811.9±1638,364	0.28
Procalcitonin	15.66±41, 0.5	6.9±30.1,0.33	0.21
C-reactive protein	123.4±86,115	125.4±108,100	0.93
Arterial blood gases			
PH	6.92±1.66,7.3	7.3±0.1,7.32	0.114
PCO2	52.8±24	65±25.6	0.014
Po2	68.4±36.7	71±23	0.66
Serum bicarbonate	26.6±8.1	28±8.2	0.39
D-dimer	2045±4390, 796	1545±2795,500	0.52
Positive cultures*			
Sputum	44 (68.75)	39 (72.2)	0.79
Blood	34 (53.1)	32 (59.3)	0.82
CT chest compatible with COVID-19	19 (29.68)	29 (53.7)	0.015

*Number and %.

AKI during the ECMO procedure (30/46 vs. 48/54) in the corresponding groups, respectively, as shown in Table 4. The mean hospital stay was comparable in both groups (31.9 ± 29.8, 28 vs. 28.8 ± 25.5,25 (P = 0.58).

After 30 days, we observed that 64 out of 120 (53.3%) patients were alive (Fig. 1). More than 63% of the survivors were discharged without oxygen support, and 36.7% needed home oxygen therapy (face mask or nasal prong), (Fig. 2).

Discussion

In patients infected with COVID-19, particularly with ECMO support, mortality is associated with multifaceted risk factors that include a combination of demographic, clinical, and laboratory parameters. Regarding severe COVID-19 patients who were indicated for ECMO support, mortality ensued in less than 50% of the patients, suggesting that ECMO was a practical approach for refractory COVID-19 critically ill patients. The study found that renal dysfunction (as represented by serum creatinine), cardiopulmonary resuscitation (before ECMO placement), and age were significant in-hospital mortality factors [17].

Table 3 Lines of management received by the studied patients

Variables	Post-ECMO survivors (*n*=64), *n* %	Post-ECMO nonsurvivors (*n*=56), *n* %	*P*
Steroids	44 (68.75)	45 (80.4)	0.18
Anticoagulants	51 (79.7)	50 (89.3)	0.11
Antiviral	10 (15.6)	10 (17.9)	0.81
Biological therapy	14 (21.9)	5 (8.9)	0.04
Antibacterial	55 (85.9)	49 (87.5)	0.50
Blood transfusion	30 (46.9)	28 (50)	0.57
Plasma transfusion	4 (6.25)	5 (8.9)	0.70

Table 4 Complications reported during ECMO procedure

Variables	Post-ECMO survivors (*n*=64), *n* %	Post-ECMO nonsurvivors (*n*=56), *n* %	*P*
Shock	35 (54.7)	50 (89.3)	<0.001
Thrombotic events	15 (23.4)	12 (21.45)	0.49
Bleeding events	19 (29.7)	24 (42.9)	0.31
AKI during ECMO	30 (46.9)	48 (85.7)	0.004

Figure 1

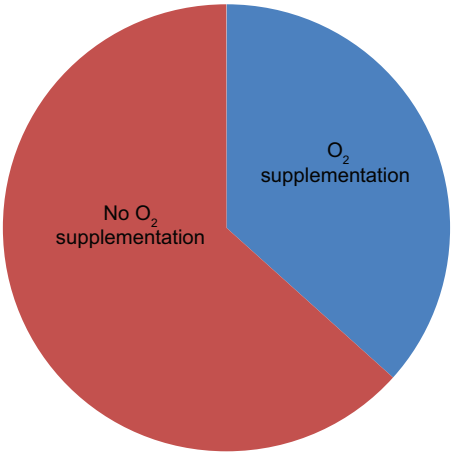
Survival rate of the studied patients.

We observed significantly higher mean age of patients of group 2 (nonsurvivors) compared with those of group 1 (the survivors) (43.6 ± 8.7 vs. 37.5 ± 10.9, respectively, P = 0.006). Patients younger than 40 years were significantly more prevalent in group 1, while the middle-aged group were more prevalent in group 2 (P < 0.05). Zhou *et al.* [18] and Kim *et al.* [19] recorded similar findings as they found that older age, admission d-dimer (more than 1 μg/ml), and elevated score of Sequential Organ Failure Assessment had higher probability of in-hospital mortality of COVID-19 patients. They added that prolonged viral shedding was also observed in nonsurvivors.

In our study, we found that most of the patients in the two groups were males (35, 54.7% vs 40, 71.4%, respectively), but without reaching significance (P = 0.059). Kim *et al.* [19] reported male gender as an independent risk factor associated ICU admission and subsequent mortality. They added some independent variables like older age, obesity, immunosuppression, and certain underlying conditions such as diabetes, neurologic disorders, renal disease, chronic lung disease, and cardiovascular disease. In our study, we found that the most prevalent COVID-19 risk factors encountered as hypertension, obesity, kidney function status, immunosuppression, COPD, and ischemic heart disease were similar in the two groups (P < 0.05) before ECMO procedure. However, diabetic patients were significantly more prevalent among group 2 patients (P = 0.024). This difference from other studies could be explained by the selection criteria adopted by our ECMO team.

We observed comparable number of patients with positive bacterial cultures in both groups (P > 0.05). Bacterial culture plays a crucial role in diagnosing and managing infections in ECMO patients, guiding appropriate antibiotic therapy [20].

Figure 2



Ventilatory support postdischarge.

Interestingly, we found that laboratory markers indicating bacterial co-infection, as evidenced by high procalcitonin, were higher in group 1 (15.66 ± 41,0.5 vs. 6.9 ± 30.1,0.33) but this did not rank to significance ($P > 0.05$). Moreover, Park *et al.* [21] reported that ECMO support did not improve survival in patients with refractory septic shock. Therefore, they suggested ECMO implantation during refractory septic shock in severe myocardial injury patients, but not in patients who received CPR. These observations and suggestions support our finding that hemodynamic instability (shock) was reported significantly more frequently in patients of group 2 (50 vs. 35 cases in group 1, $P < 0.001$).

COVID-19 is accompanied by a hypercoagulability state possibly due to increased levels of inflammatory markers, cytokine release, endothelial dysfunction, and platelet activation [22,23]. These factors contribute to the formation of blood clots throughout the body, including within the ECMO circuit. The ECMO circuit itself can trigger thrombotic events due to factors such as foreign surface exposure, turbulent blood flow, and contact activation of coagulation factors. Moreover, patients on ECMO are immobilized due to mechanical ventilation and sedation, which increases the risk of venous thromboembolism formation. Therefore, achieving optimal anticoagulation is challenging in ECMO patients with COVID-19 due to the dynamic changes in coagulation parameters, variable responses to anticoagulant therapy, and the hazard of bleeding complications [4,24].

We observed no significant difference between the studied groups regarding hematological complications (either thrombotic or bleeding events) ($P > 0.05$). This could be explained by the adopted multidisciplinary management policy in treating such groups of patients. In our cohort, we observed that diabetic patients were significantly more prevalent among patients in group 2 ($P = 0.024$). This finding highlighted the importance of diabetes control on the outcome. Bode *et al.* [25], recorded higher mortality rate among cases with uncontrolled hyperglycemia, emphasizing the need for effective inpatient hyperglycemia management.

We observed significantly higher number of patients who received biological treatment in the survivor group (21.8 vs. 8.9%, $P = 0.04$). This observation was matched with the finding of Salama C *et al.* [26], who reported a reduction in the chance of deterioration up to mortality or complex outcome of MV in ICU admitted COVID-19 patients. However, no improvement in survival was reported.

The relationship between AKI and ECMO is complex. ECMO itself can potentially cause or exacerbate AKI due to factors like altered blood flow and increased risk of clot formation. Additionally, patients who require ECMO are often critically ill, which predisposes them to AKI due to various factors such as sepsis, hypotension, and exposure to nephrotoxic medications [27,28]. In our study, we can observe that the kidney function was stable in most patients before ECMO procedure (33 out of 53 vs. 36 out of 56). Unfortunately, a higher number of patients developed AKI during the ECMO procedure (30 out of 46 vs. 48 out of 54) in the corresponding groups, respectively. This finding was matched with that reported in other studies. The outcome of AKI in ECMO-patients is governed by different factors, including its AKI, the underlying cause, the patient's overall health condition, and the type of management provided. AKI accompanying ECMO-patients is associated with higher mortality and morbidity, including prolonged length of hospital stays and subsequently higher healthcare costs [28]. In the same direction, Schmidt and colleagues have shown that AKI developed in COVID-19 patients requiring ECMO increased their morbidity and mortality. The presence of AKI complicates the management of patients on ECMO and may lead to longer length of hospital stays, increased resource utilization, and poorer outcomes [13].

In our study, we found that more than 63% of the survivors were discharged without oxygen support and 36.2% needed home oxygen therapy (oxygen mask or cannula). This observation was in accordance with other studies showing that some COVID-19 patients with ECMO support may require long-term oxygen therapy after discharge, especially if they experience residual lung damage or impaired lung function. Long-term oxygen therapy can be administered through various delivery devices, including oxygen concentrators, liquid oxygen systems, or compressed gas cylinders, depending on the patient's needs and lifestyle [12,13].

Moreover, we found the two groups were nearly similar regarding other laboratory parameters apart from higher PCO_2 in group 2 ($P = 0.014$). This agrees with Gannon *et al.* [29] in their study that highlighted a high probability of mortality in patients with higher pre ECMO $PaCO_2$. Elevated levels of CO_2 reflected more severe affection and correlated with more destructive changes in the lung's capability of manipulating gas exchange.

Conclusion

ECMO must be indicated for critically sick COVID-19 patients with respiratory failure that not

responding to SOC management. We found that young age and treatment with biological agents were good omens for survival, while the mortality risk factors were diabetes, shock, AKI during the procedure, CT findings matched with COVID-19 pneumonia, and high arterial CO_2.

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Conflicts of interest

There are no conflicts of interest.

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